

PATENT COOPERATION TREATY

NTH/WK/ams

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

KLARQUIST SPARKMAN, LLP
Attn. Rupert, Wayne
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year)	12/10/2005
Applicant's or agent's file reference 4239-6822603	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2005/019678	International filing date (day/month/year) 03/06/2005
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA	

DOCKETED FOR:

12/12/05, 11/2/06

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Gwenaëlle Llorca

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4239-6822603	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2005/019678	International filing date (day/month/year) 03/06/2005	(Earliest) Priority Date (day/month/year) 04/06/2004
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/019678

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/385

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHNEERSON R ET AL: "PREPARATION, CHARACTERIZATION, AND IMMUNOGENICITY OF HAEMOPHILUS INFLUENZAE TYPE B POLYSACCHARIDE-PROTEIN CONJUGATES" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 152, no. 2, 1 August 1980 (1980-08-01), pages 361-376, XP000674381 ISSN: 0022-1007 cited in the application page 363, line 27 - line 33 page 363, lines 36-41 ----- -/--	1-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

29 September 2005

Date of mailing of the international search report

12/10/2005

Name and mailing address of the ISA

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Authorized officer

Luyten, K

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TE PIAO KING ET AL: "PREPARATION OF PROTEIN CONJUGATES VIA INTERMOLECULAR HYDRAZONE LINKAGE" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 25, 1986, pages 5774-5779, XP001015547 ISSN: 0006-2960 cited in the application page 5775, left-hand column, line 27 - line 36 page 5775, right-hand column, line 13 - line 19 page 5775, right-hand column, line 27 - line 38	1-16
A	DEVI S J N ET AL: "CRYPTOCOCCUS-NEOFORMANS SEROTYPE A GLUCURONOXYLOMANNAN PROTEIN CONJUGATE VACCINES SYNTHESIS CHARACTERIZATION AND IMMUNOGENICITY" INFECTION AND IMMUNITY, vol. 59, no. 10, 1991, pages 3700-3707, XP002346145 ISSN: 0019-9567 abstract	1-16
A	US 4 496 538 A (GORDON ET AL) 29 January 1985 (1985-01-29) examples II-V	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/019678

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4496538	A	29-01-1985	AU 561978 B2	21-05-1987
			AU 1822783 A	08-02-1984
			CA 1210695 A1	02-09-1986
			DE 3363505 D1	19-06-1986
			DK 93584 A	23-02-1984
			EP 0098581 A2	18-01-1984
			ES 8500745 A1	01-02-1985
			FI 840874 A	05-03-1984
			IE 55268 B1	18-07-1990
			IL 69165 A	30-11-1987
			JP 2097463 C	02-10-1996
			JP 5262668 A	12-10-1993
			JP 7121872 B	25-12-1995
			JP 3047253 B	18-07-1991
			JP 59501360 T	02-08-1984
			KR 8801098 B1	29-06-1988
			NZ 204771 A	06-03-1987
			WO 8400300 A1	02-02-1984
			ZA 8304939 A	29-08-1984

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/019678

International filing date (day/month/year)
03.06.2005

Priority date (day/month/year)
04.06.2004

International Patent Classification (IPC) or both national classification and IPC
A61K39/385

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...

DOCKETED FOR: 4/4/06 ✓

1. This opinion contains indications relating to the following items

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

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CC:**

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Luyten, K

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/019678

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/019678

**Box No. V Reasoned statement under Rule 43b/s.1(a)(I) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V

1 Reference is made to the following documents:

- D1:** SCHNEERSON R ET AL: "PREPARATION, CHARACTERIZATION, AND IMMUNOGENICITY OF HAEMOPHILUS INFLUENZAE TYPE B POLYSACCHARIDE-PROTEIN CONJUGATES" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 152, no. 2, 1 August 1980 (1980-08-01), pages 361-376, XP000674381 ISSN: 0022-1007 (cited by the applicant)
- D2:** TE PIAO KING ET AL: "PREPARATION OF PROTEIN CONJUGATES VIA INTERMOLECULAR HYDRAZONE LINKAGE" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 25, 1986, pages 5774-5779, XP001015547 ISSN: 0006-2960 (cited by the applicant)

- 1.1** Document D1 discloses a method for making an immunogenic conjugate comprising a hapten or an antigen covalently linked to a carrier, the method comprising: reacting a first agent with a dihydrazide resulting in a hydrazino-modified first agent, wherein the first agent is a hapten, an antigen or a carrier (e.g. bovine serum albumin, hemocyanin, diphtheria toxin) (page 363, lines 27-33); activating a second agent with CNBr, wherein the second agent is a hapten or an antigen (Haemophilus influenzae type b capsular polysaccharide) (page 363, lines 36-39); and reacting the hydrazine-modified first agent with the CNBr-activated second agent resulting in an immunogenic conjugate comprising a hapten or an antigen covalently linked to a carrier via a hydrazone linkage (page 363, lines 39-41). The immunogenic conjugates disclosed in document D1 have the following structure: carrier - linking group - hapten/antigen, whereby the linking group contains a hydrazone and a hydrazo bond.
- 1.2** Document D2 discloses a method for making protein conjugates, the method comprising: reacting a first protein (e.g. ovalbumin) with a hydrazide resulting in a hydrazino-

modified first protein (page 5775, left-hand column, lines 27-36);
reacting a second protein (e.g. ovalbumin) with a benzaldehyde compound resulting in a benzaldehyde-modified second protein (page 5775, right-hand column, lines 13-19);
and reacting the hydrazine-modified first protein with the benzaldehyde-modified second protein resulting in a protein conjugate comprising a hydrazone linkage (page 5775, right-hand column, lines 27-38).

- 2 In the method disclosed in document D1 the second agent is activated with CNBr instead of modification with benzaldehyde as in the method of claim 1. Therefore, the linking group of the immunoconjugates of document D1 does not comprise a benzoylene moiety. In the method disclosed in document D2 a hydrazide is used instead of a dihydrazide to modify the first agent. Therefore, the linking group of the protein conjugates of document D2 contains a benzoylene moiety and a hydrazone bond, but no hydrazo bond. Thus, the subject-matter of claims 1-16 is novel in the sense of Article 33(2) PCT.
- 3 Though, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-16 does not involve an inventive step in the sense of Article 33(3) PCT for the following reasons.
 - 3.1 Document D1 is regarded as being the closest prior art to the subject-matter of claims 1-16.
 - 3.2 The subject-matter of claim 1 differs from this known document D1 in that benzaldehyde is used to modify the second agent before linking both agents. Consequently the immunogenic conjugate synthesized according to the method of claim 1 and claimed in claim 8, has a linking group comprising a benzoylene moiety.
 - 3.3 The problem to be solved by the present invention may therefore be regarded as providing an alternative method for linking two agents to produce an immunogenic conjugate, wherein the first agent is modified with dihydrazide.
 - 3.4 Document D1 discloses a method for making immunogenic conjugates wherein a

dihydrazide is used for linking an antigen or hapten to a carrier. Document D2 discloses a method for making protein conjugates wherein a hydrazide and benzaldehyde are used for linking two proteins. Therefore, the skilled person would, without the need to exercise inventive skill, be aware from document D2 that benzaldehyde can be used for modifying an agent and linking it to an agent with a hydrazino-group to make immunogenic conjugates as claimed in claim 1.

- 3.5 Therefore the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).
- 3.6 The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 8, which therefore is also considered not inventive.
- 3.7 Dependent claims 2-7 and 9-16 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

SECTION VIII

- 1 The subject-matter of claims 15 and 16 is not clear, since these entity claims refer to a method claim.